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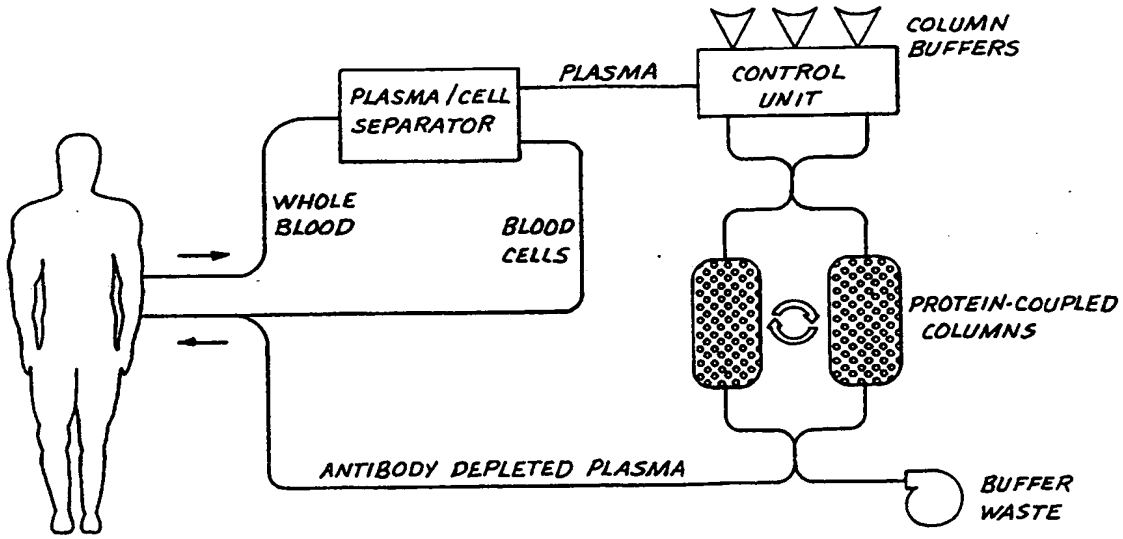

(57) Abstract

Immunoapheresis treatment for cardiomyopathy comprises passing the patient's plasma over a column having coupled thereto a specific ligand for human immunoglobulin, thereby removing a significant portion of the immunoglobulin from the patient's plasma, and then reinfusing the plasma to the patient. The invention is the use of a specific ligand for human immunoglobulin in the manufacture of a column having the ligand coupled thereto, the column being useful for immunoapheresis treatment of a patient with cardiomyopathy. The specific ligand binds, and thereby removes, human autoantibodies which are harmful to cardiac tissue such as antibodies against β_1-adrenergic receptors, ADP-ATP carriers, α and β myosin heavy chains, and adenine nucleotide translocators. Immunoapheresis treatment using the column results in improvement of hemodynamic parameters such as mean arterial pressure, mean pulmonary pressure, pulmonary capillary wedge pressure, right atrial pressure, cardiac output, cardiac index, stroke volume index, and systemic vascular resistance.

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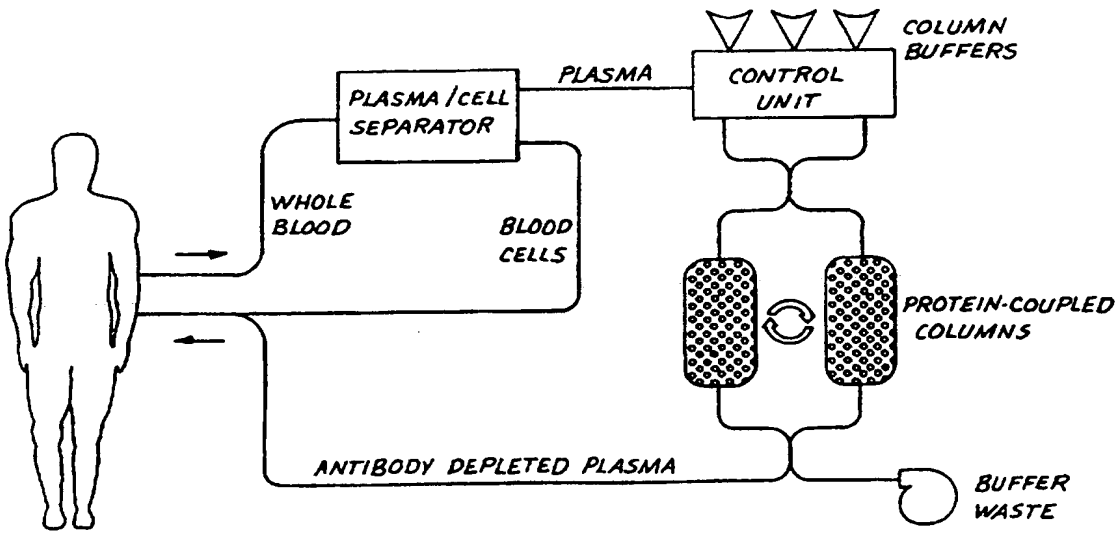

(57) Abstract

Immunoapheresis treatment for cardiomyopathy comprises passing the patient's plasma over a column having coupled thereto a specific ligand for human immunoglobulin, thereby removing a significant portion of the immunoglobulin from the patient's plasma, and then reinfusing the plasma to the patient. The invention is the use of a specific ligand for human immunoglobulin in the manufacture of a column having the ligand coupled thereto, the column being useful for immunoapheresis treatment of a patient with cardiomyopathy. The specific ligand binds, and thereby removes, human autoantibodies which are harmful to cardiac tissue such as antibodies against β_1-adrenergic receptors, ADP-ATP carriers, α and β myosin heavy chains, and adenine nucleotide translocators. Immunoapheresis treatment using the column results in improvement of hemodynamic parameters such as mean arterial pressure, mean pulmonary pressure, pulmonary capillary wedge pressure, right atrial pressure, cardiac output, cardiac index, stroke volume index, and systemic vascular resistance.

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TREATMENT OF CARDIOMYOPATHY BY REMOVAL OF AUTOANTIBODIES

Acute and chronic myocarditis is often accompanied by the prevalence of high affinity anti-beta-1 receptor autoantibodies in high titers. Like the catecholamines, these anti-beta-1 receptor autoantibodies activate the beta-adrenegic system. Possible clinical consequences include the destruction of cardial structures with subsequent cardiac insufficiency in the context of a dilatative cardiomyopathy, and persisting arrhythmias as a consequence of the sympathomimetic effect of the anti-beta-1 receptor autoantibodies.

These anti-beta-1 receptor autoantibodies correlate with the severity of dilatative cardiomyopathy. In a clinical trial, the removal of antibodies using an immunoapheresis system as described below correlated with the clinical improvement in the patients treated. Hereinafter, the term "IA" will refer to immunoapheresis using a column which has a specific ligand coupled thereto, as described below. The term "Ig-THERASORB" will refer to the column which is available from Therasorb Medizinische Systeme GmbH, Unterschleissheim/Munich, Germany. The specific Ig-THERASORB column is also described below.

Treatment with the IA system effects the removal of a high proportion of antibodies of all classes and IgG-subclasses and therefore of antibodies directed against cardiac structures, namely anti-beta-1 receptor autoantibodies. This treatment also removes antibodies of any other specificity against cardiac tissue. It is postulated that removal of these autoantibodies is the basis for the efficacy of IA treatment of patients with cardiomyopathy.

The treatment schedule foresees an initial series of IA treatments within a one or two week period, preferentially three or more IA treatments. The initial series of IA treatments can be followed by additional IA treatments if indicated as determined by autoantibody-monitoring and/or clinical symptoms.

The invention encompasses use of a specific ligand in the manufacture of a column for extracorporeal removal of autoantibodies directed against cardiac structures by removing immunoglobulins of any or all classes and subclasses, for the treatment of cardiomyopathy. Such removal can be accomplished by using any specific ligands for human immunoglobulin coupled to the IA column. Such ligands include polyclonal and monoclonal anti-human immunoglobulin antibodies, fragments of such antibodies (FAB_1, FAB_2), recombinant antibodies or proteins, synthesized peptides, Protein A and Protein G.

The invention also encompasses the use of more specific ligands in the manufacture of a column for extracorporeal removal of autoantibodies against cardiac structures, using constructs mimicking the antigen targets of the autoantibodies which are coupled to the IA column. Such antigen-mimicking molecules include anti-idiotypic antibodies (polyclonal or monoclonal), and fragments of such antibodies or synthesized peptides such as parts of receptor structures of other chemical substances.

Methods and compositions for the production of sterile and pyrogen-free protein-coupled columns are provided in WO 95/31727 entitled STERILE AND PYROGEN-FREE COLUMNS COUPLED TO PROTEIN FOR BINDING AND REMOVAL OF SUBSTANCES FROM BLOOD. This application is herein incorporated by reference, with specific reference to the enabling information contained in the following sections:

For production of antibodies and virus inactivation, Example 1. For description of pre-columns and working columns, Example 2. For sterile purification of antibodies/protein destined to be coupled to the therapeutic column, Example 3. For preparation of sterile and pyrogen-free column matrix, Example 4. For activation of column matrix material and coupling of protein thereto, Example 5. For finishing of final column product, Example 6.

Immunoapheresis in the clinical setting:
The following will describe experience with clinical immunoapheresis which can be applied to cardiomyopathy patients.

Anti-human immunoglobulin coupled columns were used for the removal of immunoglobulin from the blood of human patients suffering from idiopathic thrombocytopenic purpura (ITP), systemic lupus erythematosus (SLE), vasculitis, and sensitization to HLA. These procedures were part of controlled clinical trials carried out in Europe for the treatment of autoimmune patients whose conditions were refractory to conventional treatments, and patients in need of kidney transplant who had cytotoxic anti-HLA antibodies in their blood.

The apparatus was set up essentially as depicted in Figure 1. Briefly, the tubing system of the primary separation system was first filled with sterile 0.9% NaCl. Two anti-human Ig columns (Ig-THERASORB, initially available from Baxter Immunotherapy Division, Europe; now available from Therasorb Medizinische Systeme GmbH, Unterschleissheim/Munich, Germany) were connected with the primary separation system.

The Ig-THERASORB column has coupled thereto pooled polyclonal antibodies raised in sheep immunized with pooled human immunoglobulin plus adjuvant. The coupled antibodies bind to human light chains such as lambda and kappa light chains, and thereby recognize and bind to both human IgG and IgM. The coupled antibodies also bind to IgG heavy chain.

All tubing connections were made under aseptic conditions. To remove the preservative solution from the columns, each column was rinsed before its first use with 5 liters sterile 0.9% NaCl solution, at a flow rate of 90-100 ml/min. For each subsequent use, it was sufficient to rinse each column with 2 liters of the sterile solution, at the same flow rate.

Before start of the procedure, the entire system was tested for absence of air bubbles and leaks, correct connections of the solutions, including the anticoagulants, correct installation of the programming of the device, functionality of the automatic clamps, and the safety system.

The appropriate canulae were connected to the left and right cubital veins of the patient. Blood samples were taken. The connection to the blood cell separator was put in place.

Anticoagulation was accomplished with either heparin or citrate (ACD-A or ACD-B). When citrate was the anti-coagulant, during the first half of the procedure, the citrate was used at a dilution of 1:22 to 1:18. In the second therapy phase, the dilution utilized was 1:12 to 1:8. Symptoms of hypocalcemia were monitored (paraesthesia in fingers or lips), and the administration of citrate was

diminished accordingly. Calcium tablets could be given in cases of frank hypocalcemia.

After the venous puncture and the connection of the tubing system to the patient, the blood cell separator was filled with the patient's blood. The blood flow rate was kept between 50-90 ml/min. When a column with a volume of 100 ml was used, the liquid level was maintained at about 0.8 cm over the SEPHAROSE in the column. After the stabilization of the separation process, the cell-fee plasma was directed through the tubing system over the first column. It was important to keep the flow rate even and to monitor the plasma level over the SEPHAROSE in the column. A higher plasma level was undesirable, because it would have let to a higher volume burden for the patient, and plasma loss due to plasma retention in the column.

Using a plasma flow rate of up to 40 ml/min, the column was loaded with as much plasma as possible during 15 minutes. Thereafter, the plasma flow was switched to the second column, which was likewise filled with as much plasma as possible in 15 minutes.

During the time of filling of the second column, the plasma in the first column was flushed out using sterile 0.9% NaCl at the plasma flow rate. One column volume of plasma was returned to the patient together with the blood cells which had been removed.

Also during filling of the second column, the first column was regenerated as follows: (1) A further rinse with 50 ml 0.9% NaCl at a flow rate of 100 ml/min; (2) Desorption of the bound immunoglobulin with one column volume of sterile 0.2 M glycine/HCl buffer, pH 2.8. The controller of the device prevented contact between this solution and the patient. The desorbed immunoglobulin was discarded. (3)

Neutralization with one column volume of sterile PBS, pH 7.4. Testing of the neutralization using pH indicator paper. (4) Rinsing out of the PBS with at least one column volume of sterile 0.9% NaCl. The column was then ready for the next round of adsorption.

Then, the filling of the columns was again automatically switched. This procedure was repeated as many times as necessary to process the desired volume of plasma. The number of cycles used was chosen by the attending physician, according to the condition and needs of the patient. So far, within the inventors' clinical experience, it has been possible to process up to 3.5 times the extracorporeal volume of a given patient during one column procedure. Moreover, the number of cycles used was not limited by the binding capacity of the columns, but rather by the needs of the individual patient.

Blood samples were taken for analysis of the success of the procedure. Assays for immunoglobulin classes were performed, and tests for anti ß-1 receptor autoantibodies were done.

After each procedure, the columns assigned to each patient were cleaned and stored under aseptic conditions at 2-8°C until the next use for the same patient.

Results: Preliminary results showed that the IgG concentration in the subjects' blood was reduced by at least 70% to over 99% compared to starting concentrations. IgA and IgM levels were reduced by 70% to 90%.

There was no morbidity or mortality associated the use of the column procedure. Plasma loss was typically low, and no plasma replacement was required

Use of Immunopheresis in Treatment of Cardiomyopathy:
Previous studies have shown that sera of patients with dilated cardiomyopathy (DCM) are positive for stimulatory gamma-globulin antibodies directed specifically against the β_1-adrenergic receptor. These antibodies are extractable by immunoadsorption (IA) on a column according to the present invention. IA was performed on five consecutive days in nine patients with severe DCM on stable medication. IA caused a decrease of anti β_1-adrenergic receptor antibodies from 6.4 ± 1.3 to 1.0 ± 0.5 relative units. During IA, cardiac output increased from 3.7 ± 0.8 to 5.5 ± 1.75 l/min, $p<0.01$. Mean arterial pressure decreased from 76 ± 9.9 to 65 ± 11.2 mmHg, $p<0.05$, mean pulmonary arterial pressure from 27.6 ± 7.7 to 22.0 ± 6.5 mmHg, $p<0.05$, left ventricular filling pressure from 16.8 ± 7.4 to 12.8 ± 4.7 mmHg, $p<0.05$, and systemic vascular resistance decreased from 1465 ± 332 to 949 ± 351 dyn x s x cm^{-5}, $p<0.01$.

The cause of injury to the myocardium in DCM is unknown. Consequently, standard treatment is purely symptomatic because it cannot be specifically directed towards aetiology. In recent years evidence accumulated that autoimmunologic mechanisms may play an important role in the initiation and progression of myocardial injury in dilated cardiomyopathy. Several cardiac autoantibodies have been found in dilated cardiomyopathy. Recently it has been shown that autoantibodies directed against the cardiac β_1-adrenergic receptors are present in sera from patients with idiopathic dilated cardiomyopathy. These autoantibodies are part of the gamma-globulin fraction of patients with DCM and are able to induce a positive chronotropic effect on neonatal rat heart myocytes in culture. Chronic adrenergic stimulation appears to be an important factor in the pathogenesis of DCM. The activation of the sympathetic nervous system is know to be associated with progressive deterioration of cardiac

function and increased mortality in patients with chronic congestive heart failure. To answer the question whether anti $ß_1$-adrenergic receptor antibodies with chronotropic activity may play a role in the pathogenesis of dilated cardiomyuopathy, the IA procedure was used to remove immunoglobulin in 9 patients with severe dilated cardiomyopathy.

Nine patients (8 men and 1 woman) with severe chronic congestive heart failure refractory to medical therapy participated in the study. Their ages ranged from 25 to 58, mean age 43.5 years. All patients suffered from dilated cardiomyopathy, New York Heart Association functional class II or IV. The left ventricular ejection fraction was <25% as assessed by left heart catheterization and echocardiography. All patients were on stable medication, including ACE inhibitors, digitalis and diuretics. Because anti ß-receptor antibodies are competitively displaced by ß-blockers, patients were additionally treated with ß-blockers. Beta-blocker therapy was started one day prior to IA with esmolol (25 µg/kg/min) intravenously. Esmolol infusion was followed by oral therapy with metoprolol (mean dose 59.4 mg/day, range 25 - 100).

Right heart catheterization using a Swan-Ganz thermodilution catheter was performed to determine hemodynamic measurements. The following measurements were made four times a day: systolic and diastolic pulmonary arterial pressure, pulmonary capillary wedge pressure, mean right atrial pressure and cardiac output. The derived hemodynamic variables included: cardiac index, stroke volume index, systemic vascular resistance and pulmonary vascular resistance. Prior to IA the hemodynamic measurements showed a stable baseline of all measured parameters. 2-D echocardiography was used before and after

immunoadsorption for the assessment of left ventricular ejection fraction. LV-, RV-, and LA internal dimensions were measured by M-mode echocardiography.

After completion of baseline measurement, the immunoglobulin extractions were performed using an immunoadsorber for immunoglobulin, Ig-THERASORB. The extracorporeal treatment system consists of conventional plasmapheresis to obtain plasma, and the immunoapheresis (IA) system. Immunoapheresis was performed as described above. A plasma-separation device (plasma filter OP 05, Diamed) was used for conventional plasmapheresis. The plasma was separated at a maximal plasma flow rate of 40 ml/min, passed through the immunoadsorption column and was then reinfused. The IA system consisted of two parallel columns. Plasma was passed through one of the columns while the other was being regenerated. All patients underwent one IA session daily on five consecutive days. In each session IgG plasma levels were decreased by 20 - 30 %. Following the last IA session, all patients received an infusion of approximately 35 g polyclonal IgG to restore serum IgG levels. Anti ß-receptor antibodies were determined as previously described (Wallukat, et al. J. Mol. Cell Cardiol. 27:397-406, 1995). The antibody titers were measured after each session.

Results were expressed as mean ± SD. Comparison of measurement before and after immunoadsorption therapy were made with Wilcoxon's-tests and significance was assessed at the $p<0.05$ level.

In all patients, IA procedures were well tolerated and no major complication occurred. Immunoadsorption was effective in reducing $ß_1$-adrenergic receptor stimulating antibodies in all patients. A decrease of immunoglobulin G (from 11.5 to 1.5 g/l), immunoglobulin A (from 3.3 to 1.4

g/l) and immunoglobulin M (from 1.9 to 0.4 g/l) was detected. Simultaneously, we observed a consistent decrease of $ß_1$-adrenoreceptor stimulating antibodies (from 6.4 ± 1.3 to 1.0 ± 0.5 Units/l, mean ± SD). Heart rate tended to decrease, but not significantly (88.0 ± 23.1 to 84.0 ± 20.8 beats/min). Therapy was accompanied by a significant decrease in mean arterial pressure (from 76.0 ± 9.9 to 65.0 ± 11.2 mmHg, $p<0.05$) and mean pulmonary pressure (from 27.6 ± 7.7 to 22.0 ± 6.5 mmHg. $p<0.05$). There was a significant decrease in pulmonary capillary wedge pressure (from 16.8 ± 7.4 to 12.8 ± 4.7 mmHg. $p<0.05$), and right atrial pressure (from 9.1 ± 3.7 to 5.3 ± 3.2 mmHg, $p<0.05$). Cardiac output significantly increased from 3.7 ± 0.8 to 5.5 ± 1.8 l/min, $p<0.01$. Cardiac index and stroke volume index increased from 2.0 ± 0.42 to 2.9 ± 0.79 l/min/m, $p<0.01$ and 24.0 ± 7.4 to 35.9 ± 10.3 ml/m^2, $p<0.05$, respectively. Resulting from hemodynamic changes mentioned above, systemic vascular resistance decreased progressively (from 1465.4 ± 331.8 to 949.3 ± 351.2 dyn x s x cm^{-5}, $p<0.01$ and from 198.9 ± 56.6 to 145.4 ± 69.4 dyn x s x cm^{-5},n.s., respectively). Left ventricular ejection fraction as assessed by echocardiography failed to show a significant improvement (20 to 21.9%). LV-, RV- and LA internal dimensions were unaltered.

In two patients immunoadsorption had to be stopped during therapy because of increased body temperature, which normalized after changing the central-venous catheters.

IA has been successfully used in several autoimmune diseases. It has been shown to remove antiglomerular basement membrane antibodies in Goodpasture's syndrome, antiacetylcholine antibodies in myasthenia gravis and anti-ds DNA antibodies in SLE. Highly sensitized patients awaiting renal transplantation underwent extracorporeal

immunoadsorption to remove anti HLA-antibodies (Palmer, et al., Lancet 7:10-12, 1989).

In conclusion, the decrease of circulating ß-edrenoreceptor autoantibodies was accompanied by an improvement of invasively measured hemodynamic parameters.

Removal of other autoimmunereactive antibodies detected in DCM should also be considered as possibly efficacious. For example, antibodies against the ADP-ATP carrier were reportedly able to influence the carrier function and could impair cardiac performance. Although not measured in this study, it is probable that antibodies against the ADP-ATP carrier were also removed by the IA treatment.

In another study, patients awaiting heart transplant due to end-stage cardiomyopathy were successfully treated with IA. In at least one case, the patient's heart function was so improved that he no longer required a transplant. The patient remains stable on periodic treatment with IA.

In summary, immunoadsorption can be an alternative therapeutic principle for acute hemodynamic stabilization in the presence of circulating human antibodies against $ß_1$ receptors. Immunoadsorption can remove a significant portion of a patient's plasma immunoglobulin. Herein, the term "significant portion" refers to at least 20% of the patient's immunoglobulin. In certain cases, it is desirable to remove up to 80%, and in certain cases more than 80% of the patient's immunoglobulin.

What is claimed is:

1. Use of a specific ligand for human immunoglobulin in the manufacture of a column having said ligand coupled thereto for the treatment of a patient suffering from cardiomyopathy, said treatment comprising passing plasma of the patient over the column under conditions which effect the binding of said specific ligand to immunoglobulin in the patient's plasma, thereby removing a significant portion of the immunoglobulin from the patient's plasma, and reinfusing the plasma to the patient.

2. Treatment of a patient suffering from cardiomyopathy, said treatment comprising the steps of;

(a) providing a column having coupled thereto a specific ligand for human immunoglobulin,

(b) passing plasma of the patient over the column under conditions which effect the binding of said specific ligand to immunoglobulin in the patient's plasma, thereby removing a significant portion of the immunoglobulin from the patient's plasma, and

(c) reinfusing said plasma to the patient.

3. Use of a specific ligand as in claim 1 wherein said specific ligand is selected from the group consisting of polyclonal anti-human immunoglobulin antibodies, monoclonal anti-human immunoglobulin antibodies, a fragment of such antibodies, recombinant molecules of the antibody idiotype, synthesized peptides, Protein A and Protein G.

4. Use of a specific ligand as in claim 1 wherein said specific ligand recognizes autoantibodies directed against cardiac tissue.

5. Use of a specific ligand as in claim 4 wherein said specific ligand is an antigen-mimicking molecule selected

from the group consisting of polyclonal and monoclonal antiidiotypic antibodies, fragments of such antibodies, and synthesized peptides.

6. Use of a specific ligand as in claim 5 wherein said specific ligand is a synthesized peptide mimicking a sequence of a receptor structure.

7. Use of a specific ligand as in claim 6 wherein said receptor is the $ß_1$-adrenergic receptor.

8. Use of a specific ligand as in claim 4 wherein said autoantibodies are directed against a molecule selected from the group consisting of $ß_1$-adrenergic receptors, ADP-ATP carriers, α and ß myosin heavy chains, and adenine nucleotide translocators.

9. The treatment of a patient as in claim 2 in parallel or subsequent combination with ß-blockers, intravenous immunoglobulin, or cardiac assist devices.

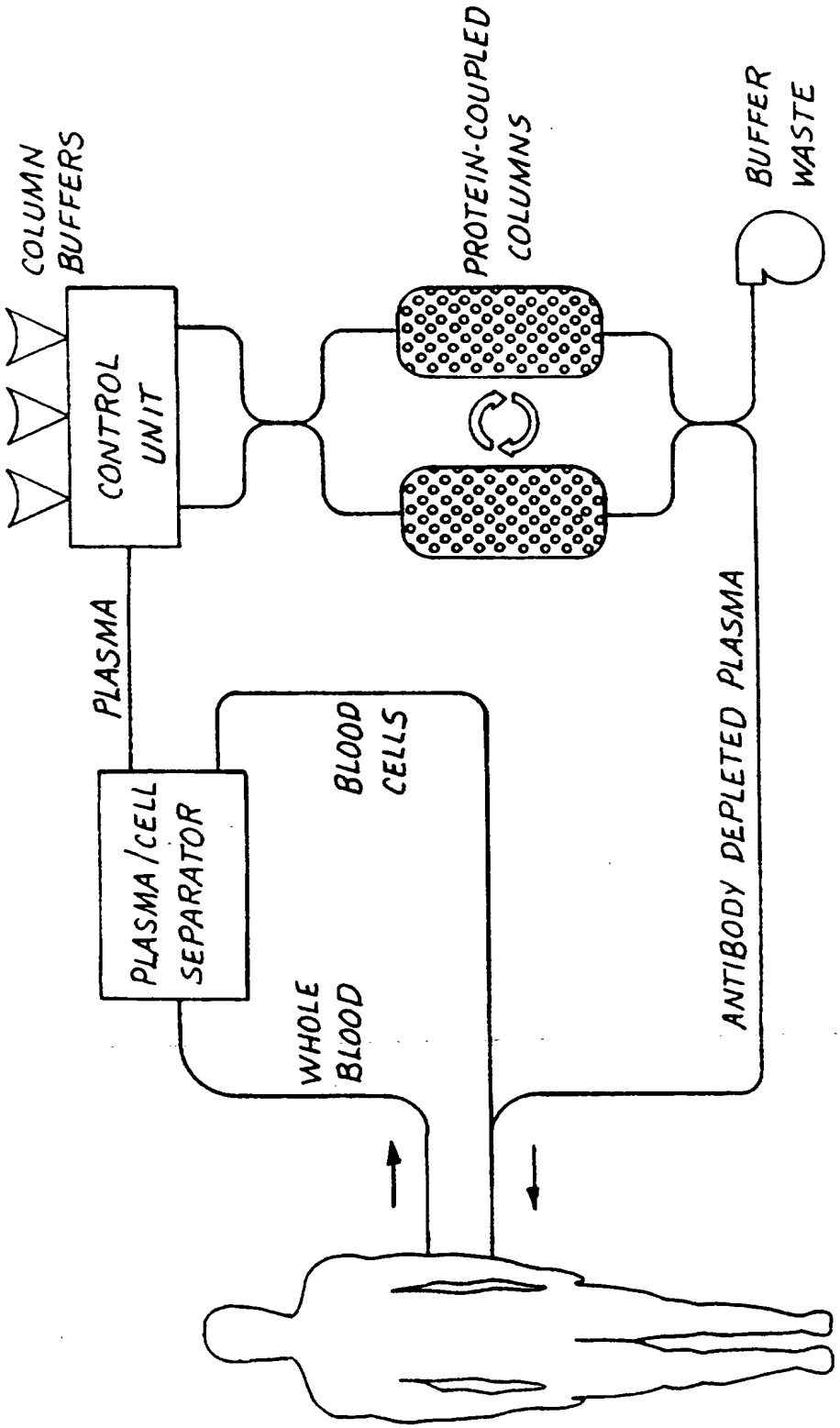

Fig. 1

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Ir. itional Application No
PCT/US 96/18457

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K35/14 //C07K1/22,A61M1/36,C07K14/72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61M A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	IMMUNOBIOLOGY, vol. 189, no. 1-2, September 1993, STUTTGART, GERMANY, page 237 XP000647618 J. MÜLLER-DERLICH ET AL.: "Extracorporeal elimination of human immunoglobulin with IgG-Therasorb." see abstract R.9 --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
24 March 1997	10.04.97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Nooij, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 96/18457

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CIRCULATION, vol. 92, no. 8 suppl., 15 October 1995, NEW YORK, NY, USA, pages 1378-1379, XP000647670 J. MÜLLER ET AL.: "Simultaneous reduction in anti-beta1 adrenoceptor autoantibodies and an improvement in cardiac function during mechanical support. An indication for weaning from assist device?" see abstract 1804	1-9
A	JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, no. special issue, February 1995, NEW YORK, NY, USA, page 23A XP000647671 J. MÜLLER ET AL.: "Reduction in beta2-receptor autoantibody level in patients with idiopathic dilated cardiomyopathy during mechanical cardiac assist system support." see abstract 901-77	1-9
A	US 4 223 672 A (TERMAN ET AL.) 23 September 1980 see column 1, line 1 - column 3, line 13	1-9
A	WO 93 24158 A (HEMAGEN/PFC & BAXTER HEALTH CARE CORP.) 9 December 1993 see examples see claims	1-9
A	WO 91 17171 A (OKLAHOMA MEDICAL RESEARCH FOUNDATION) 14 November 1991 see claims 29,30 see page 9, line 17 - page 10, line 2	1-9
P,A	WO 95 31727 A (BAXTER INTERNATIONAL INC.) 23 November 1995 cited in the application see examples see claims	1-9
P,X	INTERNATIONAL JOURNAL OF CARDIOLOGY, vol. 54, no. 2, May 1996, AMSTERDAM, NL, pages 191-195, XP000647600 G. WALLUKAT ET AL.: "Removal of autoantibodies in dilated cardiomyopathy by immunoadsorption." see page 192, right-hand column, line 39 - page 194, left-hand column, line 2	1-9

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 96/ 18457

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 2
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 2 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir. ıtıonal Application No
PCT/US 96/18457

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4223672 A	23-09-80	NONE	
WO 9324158 A	09-12-93	US 5295953 A	22-03-94
		AU 4523793 A	30-12-93
		CA 2129836 A	09-12-93
		EP 0642364 A	15-03-95
		JP 7507225 T	10-08-95
WO 9117171 A	14-11-91	AU 7958891 A	27-11-91
WO 9531727 A	23-11-95	AU 2594495 A	05-12-95
		CA 2190268 A	23-11-95